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Severe Bilateral Glossopharyngeal Neuralgia Managed With Nerve Blocks Following Plasmodium falciparum Malaria Infection Treated With Mefloquine

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Background: The Internal Classification of Headache Disorders diagnosis for glossopharyngeal neuralgia (GN) includes recurrent paroxysmal severely painful attacks in the glossopharyngeal nerve distribution. Precipitating factors may be swallowing or talking, and diagnosis is made by exclusion. Conservative management includes medications, such as carbamazepine. For refractory cases, interventional nerve blocks may be required.

Case Report: A 38-year-old woman experienced severe bilateral GN and occipital neuralgia with atypical migraines after treatment with mefloquine for severe Plasmodium falciparum malaria. Symptoms included the inability to perform activities of daily living (ADLs) due to severe "electric sharp stabbing pain." Following ineffective conservative management, she was successfully treated with a series of nerve blocks every 3 months. Over time, with repeated interventions, she acquired a significantly lower baseline of pain enabling her to participate in ADLs.

Conclusions: This case report highlights nerve blocks as a viable treatment option for refractory bilateral GN following treatment with mefloquine.

Key words: Glossopharyngeal neuralgia, malaria, plasmodium, falciparum, mefloquine, regional nerve blocks, stellate ganglion nerve block,glossopharyngeal nerve block

BACKGROUND

Glossopharyngeal neuralgia (GN) is a neuropathic disorder characterized by pain, numbness, and distribution along the sensory path of the glossopharyngeal (ninth cranial) nerve (1,2). Typically, GN presents with episodic unilateral pain with an abrupt onset and cessation in the glossopharyngeal nerve distribution, but can also involve the pharyngeal and auricular branches of the vagus nerve (CN X) (1,2). Symptoms include a severe sharp pain in the posterior oropharynx, tonsillar pillars, base of tongue, ear canal, and the angle of the mandible. Duration of pain lasts from a few seconds to about 2 minutes (1,2). Pain is typically exacerbated by chewing, swallowing, eating, coughing, yawning, or talking (1-3). The etiology of GN is commonly idiopathic in nature but can be secondary to vascular compression, mass effect lesions, inflammatory/autoimmune processes, such as multiple sclerosis, or compression from the styloid process (Eagle syndrome) (1-6). It is considered to be a highly rare cause of facial neuralgia, with a prevalence of 0.2% to 1.3 % of all types of cranial neuralgias (2). The prevalence of unilateral GN is estimated to be 0.8 cases per 100,000 people, compared to trigeminal neuralgia (TN), which has a prevalence of 4.7 cases per 100,000 (8).

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A retrospective study from Rushton et al (5) illustrated that the majority of GN cases (74%) self-resolved, 17% experienced no relief, and 12% had bilateral pain.

GN can be treated in a stepwise fashion. First-line therapy includes medical management with the most common medications being baclofen (to reduce spasms) and oxcarbazepine or carbamazepine, although other neuropathic agents, such as gabapentin, pregabalin, duloxetine, and phenytoin, are also commonly implemented (4-6). These medications should be started at low doses and titrated as needed based on their effectiveness and tolerability to side effects, while keeping within maximum recommended doses (5). The disease tends to present as a relapsing-remitting course, and medications should be tapered down to a low-maintenance dose. It is also recommended to combine 2 or more medications with different mechanisms of action to help achieve superior pain relief while mitigating side effects (5). Adjuvants, such as physical therapy and psychiatric counseling, can all be used as a multimodal approach (5).

In the event that conservative management proves ineffective in the management of GN, interventional treatments, such as glossopharyngeal and stellate ganglion nerve blocks, are treatment options THAT may be used as a diagnostic and therapeutic modality to treat this condition (5,6,8). Here, we present the case of a 38-year-old woman who is being successfully treated with bilateral regional blocks for severe atypical GN that developed following malaria infections. This case report aim to highlight the development of bilateral GN after a suspected adverse reaction to mefloquine that was used to treat a severe Plasmodium (P.) falciparum malaria infection and the utilization of nerve blocks for supplemental treatment when conservative management proves to be subsatisfactory.

CASE PRESENTATION

We report a case of a 38-year-old woman, a primatologist who experienced severe bilateral GN and occipital neuralgia associated with migraines after being treated for a severe P. falciparum malaria infection, in April 2016, during work in Cross River State, Nigeria, Africa. Her history included an uncomplicated course of P. vivax and dengue fever (2011), a previous exposure to tuberculosis in 2014-2016, and paratyphoid B (2016), with no other significant medical history. The patient's P. falciparum malaria symptoms entailed fevers, chills, diaphoresis, dry cough, confusion, and lethargy. Neuropathic symptoms, however, developed on the first day - 12 hours into treatment with mefloquine (750 mg) (first week of May), and progressively worsened. She completed 3 days of the full treatment as directed on May 5. Her initial symptoms were a severe headache on the first day, with numbness in her mouth, lips, tongue, face, ears, scalp, head, neck, shoulders, and low back on the second day. On the third day, the numbness in these regions progressed to paresthesias, and she also experienced vertigo and heart palpitations. A week later, about 8 days (192 hours) after starting mefloquine and cleared of P. falciparum parasitemia, her headache and paresthesia pain increased substantially (9-10/10), with additional onset of facial and left upper and lower extremity weakness (2-3/5 strength) along with vertigo, ataxia, and bradycardia, in addition to dysphagia and issues speaking with a hoarse voice and loss of taste. The following morning of May 11, she acquired medical treatment in Calabar, Nigeria, where she was treated in a clinic with a tapered dose of 100 mg intravenous (IV) hydrocortisone to 20 mg, 3 times daily, to a low-dose oral prednisone that 2 months later was transitioned to carbamazepine. It was initially suspected she was afflicted by mefloquine neurotoxicity (post-mefloquine effect). Immediately after treatment with IV hydrocortisone, the patient reported to have regained some mobility and strength in her face and extremities; however, weakness (3-4/5 strength in her left-sided extremities) persisted for about 2-3 years. For example, she reported shuffle walking and issues carrying objects in her left upper extremity. Throughout this time (on steroids most notably), she reported that her ability to swallow became worse, her head and face felt persistently "fatigued and heavy," with a "drooping" sensation, and difficulty holding her head up. Her severe migraines, facial, throat, and tongue pain, and paresthesias also persisted resulting in issues communicating and coping with the excruciating pain. On physical examination, it was also reported that she exhibited tongue and uvula deviation. For 1-2 years after the initial insult, she also endorsed symptoms of amnesia, confusion, disorientation, and problems with word findings.

Since the patient's initial onset of migraines, and facial, tongue, and throat neuropathy, in 2016, her head and facial neuropathic symptoms continued with constant excruciating pain. She describes difficulty in speaking, chewing, and consuming food and liquids due to severe bilateral throat, tongue, oral, and ear pain and paresthesias. Her head and neck episodic spasms

lasted from seconds to minutes and were described as debilitating "electric-sharp-stabbing pain" to the point where she developed an aversion to speaking, eating, and drinking resulting in unintentional weight loss, avoidance of socializing, and requiring leave from work. Along with migraines, her facial and neck symptoms were not exacerbated by facial palpation and were consistent with the dermatomal distribution of bilateral GN. Symptoms were also worsened by physical exertion, driving, cold temperatures, and wind on her face. After periods of talking, her voice would become noticeably raspy and hoarse. She also noted, despite seeing multiple specialists throughout the years, no clear etiology of her neuralgia was uncovered and her symptoms further progressed despite treatment to the point she was unable to work or perform activities of daily living (ADLs). Head magnetic resonance imaging scans excluded any evidence of a vascular or mass lesion. A spinal tap was also done, which was unremarkable and negative for any malaria parasite. Blood work was positive for antinuclear antibodies and an electroencephalogram illustrated occasional right temporal lobe sharp activity with slowing signal abnormalities. Swallow studies showed slowing of her esophageal peristalsis and diminished larynx movement in her first study (2021), but esophagogastroduodenoscopy biopsies had no abnormalities. Vestibulocochlear nerve testing found bilateral high-frequency hearing loss, more pronounced on the left. Facial nerve testing showed abnormal function of her stapedial branch of the left facial nerve. Holter monitoring found premature ventricular contractions associated with GN spasms and a videolaryngoendoscopy exhibited periodic vocal cord dysfunction with incorrect bilateral paramedian positioning following periods of prolonged speech and exertion. After consulting with neurologists, and infectious disease and palliative care specialists, regarding her neuropathy, she was referred to our clinic in 2019. Initial management progressed from medications to also including interventions. Overall, her treatment up to 2021 included continuing carbamazepine along with pregabalin, baclofen, acupuncture, dry needling, occipital and infraorbital nerve blocks, bilateral occipital cryoablation, cervical facet injections, facial and botox injections every 12 weeks, a temporary 10-day course of prednisone, counseling, and physical therapy. The patient responded favorably to the temporary course of steroids, occipital and cervical nerve blocks, and cervical facet injections. Superficial botox injections (administered around her occipital, temporal, and parietal lobes) and cryoablations significantly improved her migraines and occipital neuralgia, but her severe bilateral facial, tongue, and throat "spasms of pain and paresthesias attacks" associated with difficulty speaking and consuming liquids and food remained.

A series of in-office, ultrasound-guided (extraoral) glossopharyngeal and stellate ganglion nerve blocks with light sedation, standard monitoring, and supplemental oxygen were trialed. Unilateral injections on each respective side were pursued days apart. The nerve blocks initially offered 60% to 50% relief (pain score 9/10 to 5/10 after the injections) with a gradual return of pain to baseline by 3 months. After each subsequent round of injections, the patient's overall pain continued to progressively improve to a lower baseline (Figs. 1-4). After multiple rounds of nerve blocks, her baseline GN pain has significantly decreased from 9/10 (2021) to 3-5/10 (2023) (Fig. 1). Furthermore, the patient reports that only the glossopharyngeal and stellate ganglion nerve blocks resulted in a significantly decreased number of GN spasms per day (Figs. 2-4). The patient would acquire single-sided injections of dexamethasone and 0.5% bupivacaine, 5 mL solution for the unilateral glossopharyngeal, and 5 mL for the stellate ganglion block. A few days later, she would return for treatment to the contralateral side. Discomfort would gradually return back to baseline approximately 3 months later prompting the need for repeat injections (Figs. 1-4). Following treatments, the patient was very satisfied, and was able to consume denser foods and liquids, speak effortlessly for longer periods of time, was able to return to work, and perform ADLs. In addition to her routine stellate ganglion and glossopharyngeal nerve blocks, she is maintained on cerebral botox injections every 12 weeks, oxcarbazepine 150 mg tid, baclofen 5 mg qhs as needed, nortriptyline 30 mg qhs, and rimegepant 8 tablets, as needed, monthly. All together, her regimen has provided significant relief from her original symptoms; allowing her to regain functional status and continue her work in humanitarian projects and primate work in Africa.

DISCUSSION

Patients with chronic facial pain can often be difficult to treat. Given the complexity of facial innervation and nearby surrounding structures that are common sources of pain, such as dental roots, ear canal, and sinus cavities, there are many sources of pain that may present with

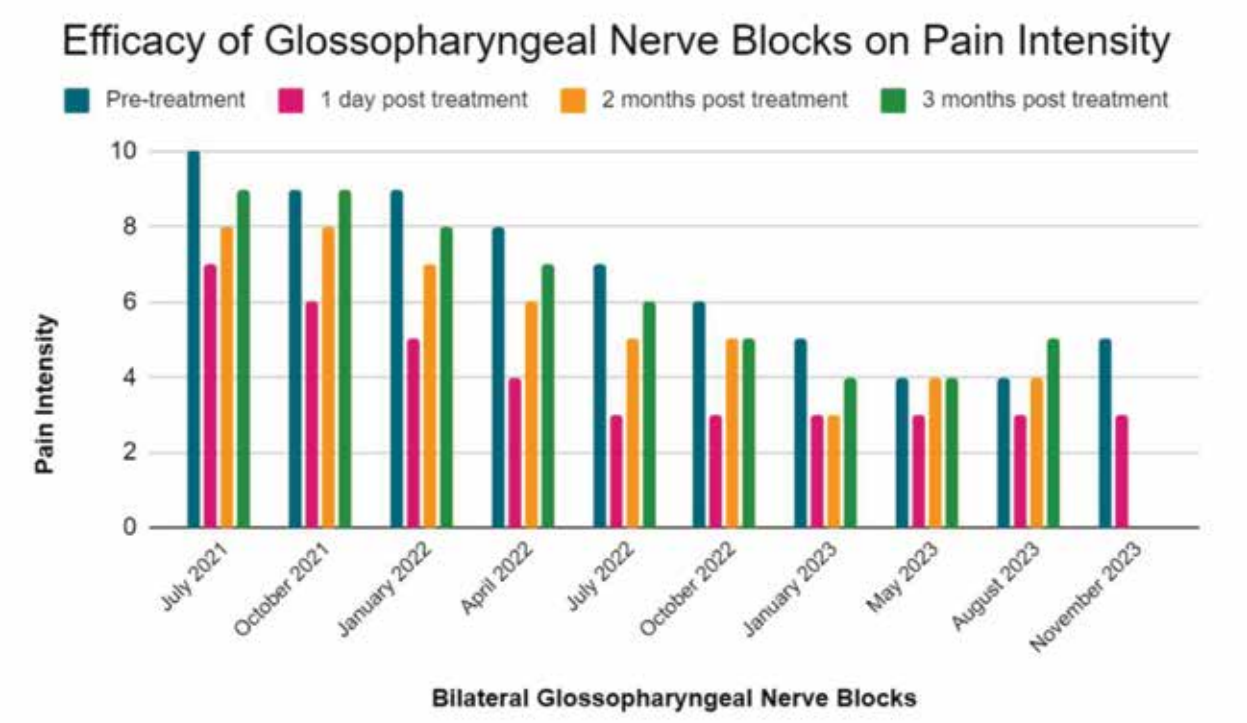

Fig. 1. Patient recorded efficacy of bilateral glossopharyngeal nerve blocks.

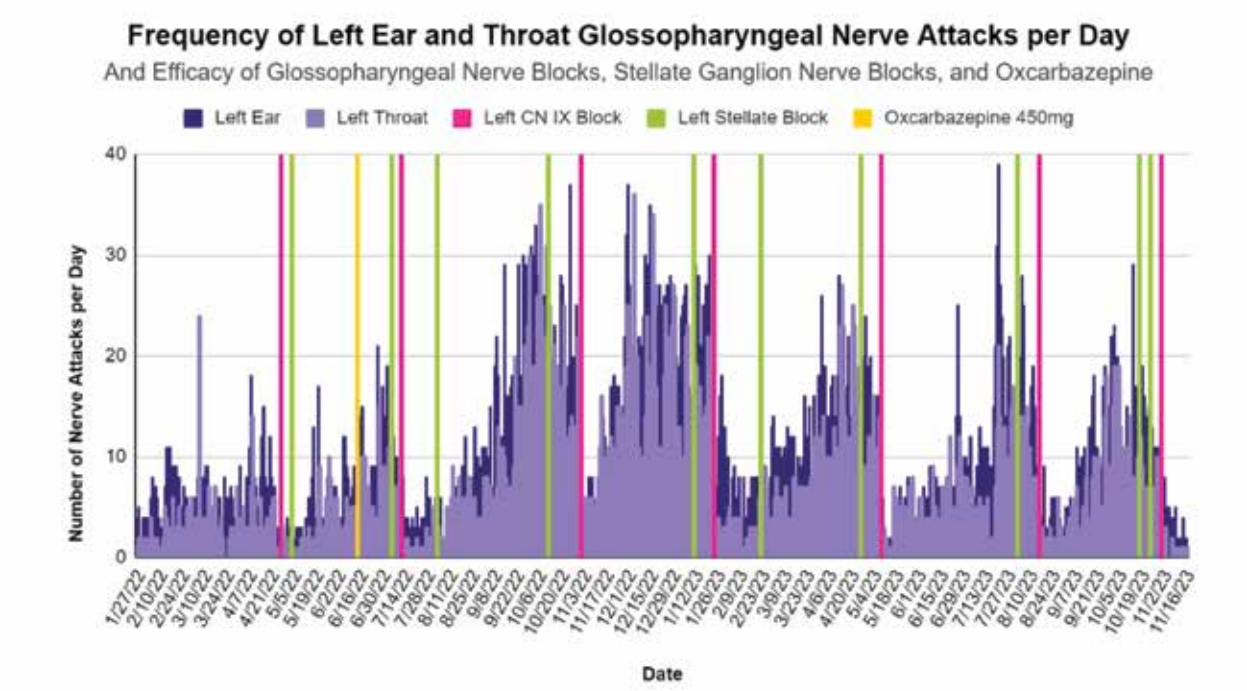

Fig. 2. Patient recorded frequency of GN spasms; along with glossopharyngeal nerve blocks and oxcarbazepine use. GN: glossopharyngeal neuralgia.

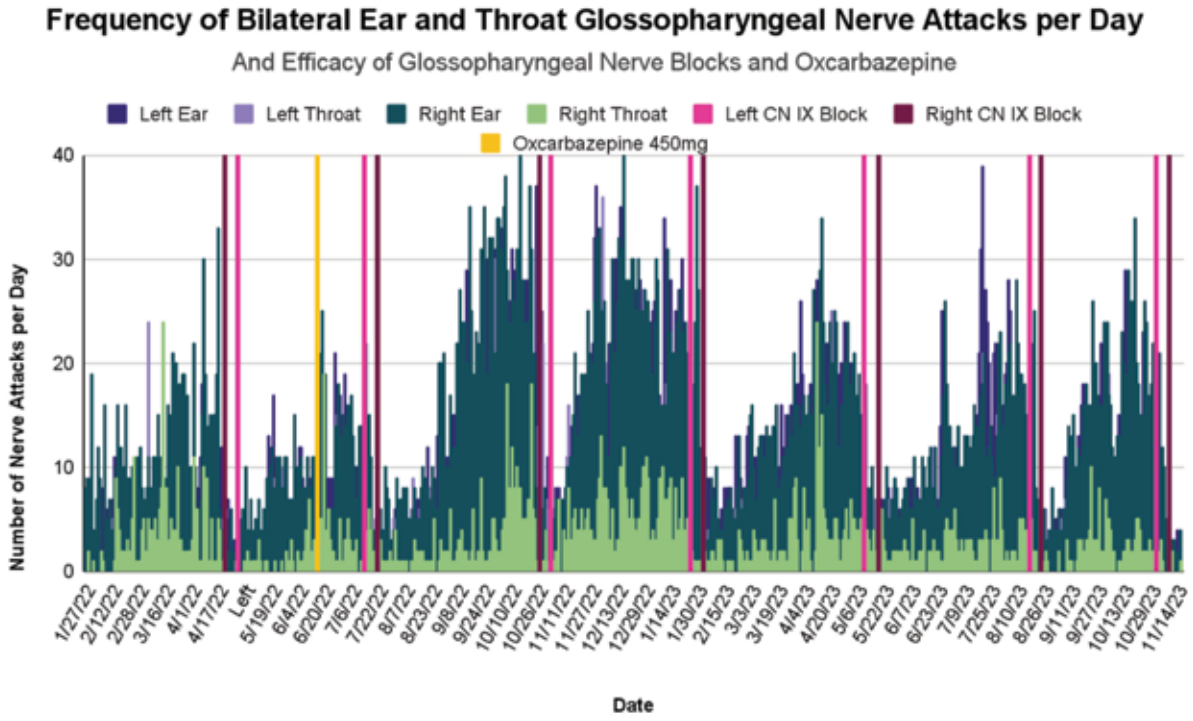

Fig. 3. Patient recorded frequency of left ear and throat glossopharyngeal nerve attacks per day. In addition to the efficacy of glossopharyngeal and stellate ganglion nerve blocks and oxcarbazepine.

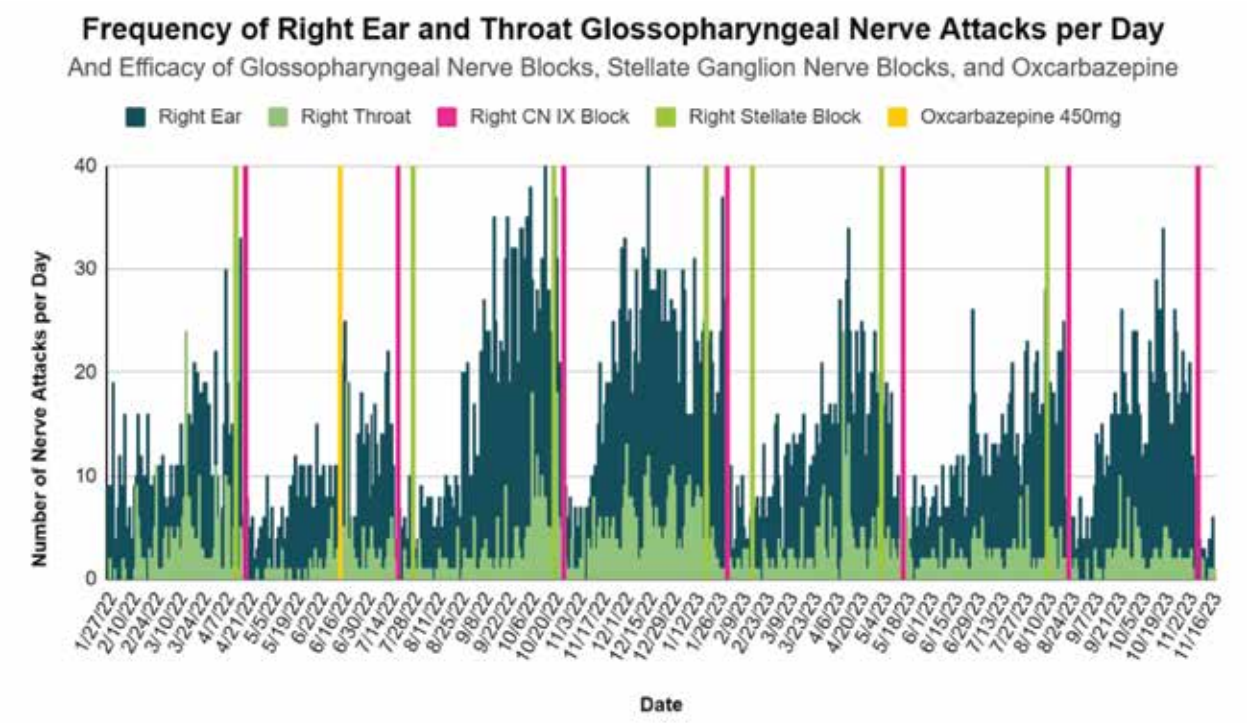

Fig. 4. Patient recorded frequency of right ear and throat glossopharyngeal nerve attacks per day. In addition to the efficacy of glossopharyngeal and stellate ganglion nerve blocks and oxcarbazepine.

similar symptoms (1,2,7). For example, GN is commonly mistaken for TN due to similar pain characteristics and pathophysiology (1,2,7). GN and TN can even co-exist; however, the incidence of GN is reported to be 1/1,000 times < TN (1). GN symptoms primarily effect the throat and tonsillar region, with pain being exacerbated from swallowing, yawning, speaking, and chewing vs TN with facial pain in the trigeminal nerve distribution (5,7). TN pain is typically exacerbated by facial touch and pressure (1). GN presents with approximately 0.8 cases per 100,000 people in one year, compared to TN, which has a prevalence of 4.7 cases per 100,000 (9). A retrospective study from Rushton et al (5) illustrated that the majority of GN cases (74%) self-resolve; however, 17% experienced no relief, and 12% had bilateral pain (5). GN has a variable prognosis based on the patient's symptoms (1).

According to Shah et al (1), most of the patients have a single episode of painful paroxysmal attacks, with an annual recurrence rate as low as 3.6%. Only 25% of patients require surgery, and the rest are successfully treated medically (1). Less than one in four patients will have bilateral pain (5). Our patient has an atypical and severe form of GN, in addition to experiencing occipital neuralgia and migraines, which further highlights how rare her condition is. She would also have multiple episodic GN spasms throughout the day, with the highest recorded being up to 40 spasms in one day (Fig. 2).

Our patient aligned with the diagnoses of GN due to exhibiting episodic electric-like spasms with chewing, speaking, and swallowing to the point where she developed an aversion to food and had severe issues speaking, and coping with the pain to the point where she struggled performing ADLs. Furthermore, our patient suffers from the rarer bilateral GN vs unilateral pain. According to Kerkar et al (2), bilateral pain with multiple bouts of severe excruciating and constant pain are poor prognostic indicators, which likely explains why our patient required interventional forms of treatment, such as routine nerve blocks in addition to medication management. Our patient is undergoing routine glossopharyngeal and stellate ganglion nerve blocks every 3 months with a unilateral side completed at her initial appointment and the contralateral side completed days later. There are 2 common approaches to block the glossopharyngeal nerve, the intraoral and extraoral. The extraoral approach is preferred due to its safety profile (2). Complications are not uncommon with glossopharyngeal nerve blocks. Intravascular injection can occur due to the vicinity of the internal jugular vein and the carotid artery (2). Another complication is the concomitant block of the recurrent laryngeal nerve, which may cause hoarseness of the voice (2). Therefore, simultaneous, bilateral glossopharyngeal nerve blocks are avoided to prevent complete vocal cord paralysis (2). Blockade of the CN X and its parasympathetic fibers may also result in tachycardia and hypertension (2). Using an ultrasound-guided extraoral approach with constant visualization of the needle will help mitigate side effects of the procedure. The patient did not experience the above adverse effects following the interventions. Stellate ganglion blocks were also performed under ultrasound visualization, with an in-plane approach. The needle was guided from a lateral-to-medial approach targeting the Chassaignac's tubercle: C6-transverse process, where medication traverses along the paravertebral fascia to reach the stellate ganglion. The stellate ganglion block targets the sympathetic chain of the ipsilateral head, neck, upper extremity, and thorax (10). Therefore, a successful block will illustrate Horner's syndrome: ptosis, anhidrosis, miosis, and scleral injection on the ipsilateral side (10). Our patient is still managed on medications as aforementioned; however, after receiving multiple rounds of routine nerve blocks, her baseline GN pain score has significantly decreased from 9-10/10 to most recently, in 2023, to around 3-5/10.

GN is a commonly misdiagnosed neuropathic disorder, which can be idiopathic in nature or secondary to an insult, such as a mass lesion or infections: tonsillitis, pharyngitis, petrositis, arachnoiditis, parapharyngeal abscess, and tuberculosis (7). In our case, we report a rare presentation of the disease following treatment with mefloquine for a severe P. falciparum malaria infection. The primary etiology of her remaining neuropathic syndrome - GN and migraines is not entirely clear even among the neurologists and infectious disease specialists she's seen, but mefloquine neurotoxicity is suspected along with the malaria infection itself. Parasite sequestration in cerebral microvasculature is thought to be a central factor in pathogenesis, and the resulting pathophysiological changes in tissue around the sequestered parasites may explain why an intravascular parasite may cause neural dysfunction and why some patients may have a poor outcome (11). There are also several neurological syndromes associated with malaria, particularly P. falciparum and P. vivax (9,12). Examples of syndromes may include postmalaria neurological syndrome, delayed cerebellar ataxia, acute inflam-

matory demyelinating polyneuropathy, Miller Fisher syndrome - a variant of Guillain-Barré syndrome/acute disseminated encephalomyelitis, posterior reversible encephalopathy syndrome, reversible cerebral vasoconstriction syndrome, malarial retinopathy, and cerebellar ataxia (9,12). Typically the aforementioned conditions resolve with care within 2-8 weeks (9). Our patient's symptoms appeared concomitantly with mefloquine use and have persisted long after the P. falciparum infection. Mefloquine can cause neuropsychiatric adverse effects, such as dizziness, vertigo, tinnitus, loss of balance, anxiety, depression, paranoia, hallucinations, and psychosis (13,14). In rare cases, studies (13,14) have shown adverse reactions may also occur after discontinuation of the drug and there are reports of mefloquine-induced neuropathy associated with pain and paresthesia. These adverse reactions may occur early in the course of mefloquine use and usually self-resolve once discontinued, but, in some cases, adverse reactions, such as anxiety, paranoia, and depression to hallucinations and psychotic behavior, have been reported to continue for months or years after mefloquine has been stopped (13). Depersonalization, confusion, concentration and cognitive problems, problems with word finding, disorientation, and symptoms of amnesia have also been noted with mefloquine toxicity, which our patient also experienced (15). Neurocognitive sequelae can also occur after P. falciparum infections.

The European Medicines Agency even noted a "strong suspicion" that mefloquine could, in some cases, cause "permanent brain damage" (13). Of note, although our patient did suffer frustration from her severe neuropathy - bilateral and refractory GN with migraines, she denies any uninstigated psychiatric or behavioral issues that arose during mefloquine. Since her condition has been most effectively managed with a multimodal approach, including interventional nerve blocks, she no longer experiences severe frustration.

Although the root cause and persistence of this patient's bilateral GN and occipital neuralgia along with migraines is atypical, her diagnosis of GN was identified and confirmed via targeting the glossopharyngeal nerve with injections; she is responding effectively to her treatments. Overall, the patient is very satisfied with her current treatment regimen and acquires the most relief from the interventional nerve blocks. Since starting the scheduled nerve blocks, she has regained the ability to consume foods/liquids and continues her humanitarian projects and primate work in Africa, and, most importantly, living her life.

CONCLUSIONS

This case report highlights multiple rare and unique presentations of a severe form of bilateral GN that is also associated with occipital neuralgia and migraines. Furthermore, it is speculated that the etiology of her atypical presentation is due to mefloquine neurotoxicity when it was used to treat a severe malaria - P. falciparum infection. This case report also highlights that extraoral glossopharyngeal nerve blocks and ultrasound-guided stellate ganglion nerve blocks offer a safe and effective treatment in refractory bilateral GN.

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